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09/641,471	08/18/2000	Carol M. Kinoshita	10278-017001	6615

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EXAMINER
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ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 04/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,741	QUINN, KERRY E.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-183* is/are pending in the application.

4a) Of the above claim(s) *81-104 and 172-183* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105-171* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 81-183 are pending.

Election/Restriction

Applicant's election with traverse of Group II, claims 105-171, in Paper No. 9 filed February 8, 2002 is acknowledged. The traversal is on the ground(s) that "the Examiner asserts that groups III and (I, II and IV) are related as product and process of use. In fact, groups III and II, as well as groups III and I, are related as product and process of making the product" (page 1). The way the claims are written, given the entire scope of the claims and the lack of the definition of "hmGCB", the claims of Group II can be construed as both, method of making and a method of use. A method comprising treating the cell expressing GCB with different compounds affecting GCB composition can be construed as a method of use of a GCB produced by a cell in a process comprising said treatment.

If inventions II and III are construed as process of making and product made, the inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the prior art teaches the production of hmGCB (e.g., Martin et al., form PTO-1449 filed February 8, 2002, reference AM).

Applicants further argue with regard to the restriction between the non-elected groups. These arguments will be addressed in more detail when the groups in question will be elected. For example, applicants argue that "the Examiner has not established that either (a) the compounds of group III can be used in a materially different process than those of group IV, or (b) the method of using of group IV can be practiced with another materially different product" (page 1). This is not agreed with because the compounds of group III can be used for the treatment of Gaucher disease and for the production of an antibody, for example. As mentioned above, the issues relevant specifically to the non-elected groups will be revisited at the time they are elected.

The requirement is still deemed proper and is therefore made FINAL.

Claims 81-104 and 172-183 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups I, III and IV, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 105-171 are under consideration.

Specification

The use of the trademark has been noted in this application on pages 23; 24; 41-45; page 51, line 16, for example. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Applicant is advised that should claim 129 be found allowable, claim 144 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 105-171 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a method of use of a cell comprising a genus of a glucocerebrosidase (GCB), with claims 127 and 128 reciting an exogenous nucleic acid sequences comprising a GCB coding region, with claim 128 further limiting to an exogenous regulatory sequence. Claims 139-171 recite a cell comprising an exogenous regulatory sequence without specifying whether a GCB coding sequence is exogenous or endogenous. Therefore, the claims comprise the genus of cells both naturally-occurring and recombinant comprising either endogenous or exogenous GCB from any source.

The specification teaches only a single representative species of such cells, human HT-1080 cells that produce Gene-Activated GCB (GA-GCB). Assuming that said cells express a human GCB, the specification does not teach an amino acid structure of said gene whereas it is known that humans have various allelic variants of GCB genes (e.g., Beutler et al., 1992). Furthermore, there is no description of how many carbohydrate chains the human unmodified GCB has and what is their carbohydrate composition. The art teaches that the oligosaccharide chains of animal glycoproteins are attached via N-glycosidic linkage to an asparagine (Asn) residue

(Bergh et al., US Patent 4,925,796, column 1, lines 38-55, form PTO-1449 filed November 30, 2000, reference AA). Two, three or four oligosaccharide chains are attached to the invariant core pentasaccharide $Man_3GlcNAc_2$ (ibid., column 3, lines 34-38). Therefore, the genus of GCBs expressed by cells used in the instant methods, encompasses GCBs from various sources, i.e., having different amino acid structures and different carbohydrate compositions. The genus of the GCB genes encompasses different structures defined by their functionality of encoding GCB. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of expressing a GCB. With regard to claims 127, 128 and 139-171 reciting an exogenous coding and/or regulatory sequence, there is no description of any GCB gene. Specifically, there is no description of any GCB gene into which said regulatory sequence can be integrated. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 107, 108, 119, 121-126, 141, 142, 151, 152 and 158-162 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cell comprising a human GCB remodeled to contain terminal mannose residues

using mannosidase inhibitors, does not reasonably provide enablement for a GCB from any source and any structure and carbohydrate composition remodeled by preventing the removal of the specific number of mannose residues and at specific locations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

For the reasons discussed above, the claims read on a method of use of a cell comprising a GCB of any structure and carbohydrate composition that is treated to produce a hmGCB. Claims 107, 108, 141 and 142 require the prevention of removal of one α 1,3 mannose or one α 1,6 mannose residue. Claims 119, 121-124 and 158-162 require the prevention of removal of a specific number of mannose residues at any positions to yield the hmGCB preparation having a requisite percent of the specific number of mannose residues. The resulting hmGCB is claimed to have at least one

carbohydrate chain with a specific number of mannose residues such as five, etc. It is clear that to produce the precise remodeling, or "trimming" of carbohydrate chains, one skilled in the art should know the mechanism and kinetics of the underlying enzymatic reaction. Enzymatic reactions are specific to substrates and reaction conditions. In the instant case the substrate is a GCB and the enzyme is a mannosidase.

Without knowing the structure of GCB and mannosidase or a type of cell comprising them, it is unpredictable under which conditions the resulting "hmGCB" can be obtained. Without the knowledge of the kinetics of the specific reaction, it is impossible to set up the conditions under which removal of only one residue at the specific position will be prevented and the preparation comprising the requisite percent of the specific number of mannose residues will be obtained.

Furthermore, claims 107 and 108 require the prevention of removal of α 1,3 mannose or α 1,6 mannose using kifunensine wherein the prior art teaches that kifunensine might prevent the removal of α 1,2 mannose (Bergh et al., *supra*, column 11, lines 24-26). With regard to claims 141-142, the specification does not teach a compound that would specifically prevent the removal of α 1,3 mannose or α 1,6 mannose.

With regard to claims 125-126 and 151-152, the specification is enabled only for cells which comprise a class 2 processing mannosidase of a known structure. Without

knowing the structure of a mannosidase, it is impossible to make a knockout gene or an antisense molecule.

The specification teaches the preparation of GCB comprising high mannose glycans such as $Man_9GlcNAc_2$ (31.2%), $Man_8GlcNAc_2$ (32%) and $Man_7GlcNAc_2$ (23.3%) using HT-1080 cells treated with kifunensine (page 55, Table 3).

This result is specific for the specific reaction occurring in these cells under the specific experimental conditions. It is unpredictable as to how many mannose residues will retain on a GCB present in a different type of cell under the same conditions. Thus, searching for conditions and substances that would lead to obtaining a hmGCB specifically quantitatively remodeled using any cell comprising any GCB is well outside the realm of routine experimentation and predictability in the art of success is extremely low. One skilled in the art would require additional guidance, such as information regarding the structure and carbohydrate composition of a GCB used as a starting material and a cell comprising thereof as well as specific conditions under which removal of mannose residues at specific positions is occurring in time. Without such a guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 105-171 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "GCB'. Applicants refer to published structures for references. As an essential material those structures cannot be incorporated by reference (page 27). The specification does not define the number and composition of carbohydrate chains of an unmodified GCB. Further, the specification defines the term "hmGCB" by non-limiting examples (page 15, line 25 through page 16, line 22) rendering the metes and bounds of the term unascertainable.

Claims 119 and 158 recite "at least about 60% of the hmGCB of the preparation have one or more carbohydrate chains in which the removal of one or more mannose residues distal to the pentasaccharide core has been prevented" (emphasis added). Depending on the number of carbohydrate chains and the number of mannose residues, the percent will vary, rendering the reference to 60% confusing and the metes and bounds of the claims unascertainable.

Claims 121-123 and 159-161 recite "at least about 20% [40%, 60%] of the hmGCB of the preparation have one or more carbohydrate chains having at least eight mannose residues" (emphasis added). Depending on the number of carbohydrate chains, the percent will vary rendering the metes and bounds of the claim unascertainable. It further renders unclear the difference in scope among these claims.

Claims 124 and 162 recite "at least about 80% or more of the carbohydrate chains of the hmGCB of the preparation have six or more mannose residues". Because the number of carbohydrate chains and the number of mannose residues are undefined, the metes and bounds of the claims are unascertainable.

Claim 139 reads on any regulatory sequence that can be incorporated into any gene not necessarily the GCB gene, that for any reason, directly or indirectly can affect the expression of an endogenous GCB.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 105, 106, 109-124, 132-135, 137 and 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aerts et al. in view of Smith et al.

Aerts et al. (form PTO-1449 filed November 30, 2000, reference AF) the production of high mannose GCB in the human monoblast cell line U937 using trimming inhibitors swainsonine or deoxymannojirimycin. They teach that swainsonine is an inhibitor of mannosidase II whereas deoxymannojirimycin is an inhibitor of

mannosidase I (page 454). They teach the importance of hmGCB preparation for efficient routing of the GCB to lysosomes (pages 456-457).

Smith et al. (US Patent 5,939,279) teach the method of preparing high mannose $Man_9(GlcAc)_2$ glycopeptides by treating a cell with mannosidase II inhibitors, deoxymannojirimycin or kifunensine (columns 7-8, column 9, claim 8). With regard to claims 109 and 110, Smith et al. teach the required range of the kifunensine concentration (column 8, lines 24 and 25). With regard to claims 111-114, Smith et al. teach the required range of the swainsonine concentration (column 8, line 26).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use either deoxymannojirimycin or kifunensine alone or in combination with swainsonine in a method taught by Aerts et al. Kifunensine can be used instead of deoxymannojirimycin in said method in view of the teachings of Smith et al. on their equivalence for that purpose.

Claims 105, 106, 109-118, 125, 126 and 129-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aerts et al. in view of Smith et al. and further in view of Bergh et al.

The teachings of Aerts et al. and Smith et al. are outlined above.

Bergh et al., *supra*, teach the structure of a high-mannose Asn-linked oligosaccharide, $Man_9GlcNAc_2$ (Figure 1B). They further teach that four of the mannose

residues of $Man_9GlcNAc_2$ are bound by α 1,2 linkages and they can be removed by mannosidase I (column 2, lines 58-68). They further teach that deoxymannojirimycin, an inhibitor of mannosidase I, prevents removal of α 1,2 (column 11, lines 24-26) and swainsonine, an inhibitor of mannosidase II, prevents removal of α 1,6 mannose (column 11, lines 26-29).

They further teach that "another approach for manipulating the structures of the N-linked oligosaccharides of a glycoprotein is to express it in cells with one or more mutations in the oligosaccharide processing pathways. Such mutations are readily selected for in mammalian cells. ... DNA coding for a glycoprotein can be introduced into such a mutant cell line using conventional methods. ... Alternatively, a mutant subline with defective processing can be selected from a line already capable of producing a desired glycoprotein. ..." (column 11, line 57, through column 12, line 32).

Therefore, at the time the invention was made, the importance of remodeling GCB to produce hmGCB has been known. The mannosidase inhibitors as tools to prepare hmGCB have been known. The genetic manipulation of protein expression and techniques to make a knockout gene and antisense molecule were known.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use kifunensine alone or in combination with swainsonine in a method taught by Aerts et al in view of teachings of Smith et al. It would have been

obvious instead of using of swainsonine to use a cell that is a knockout for a mannosidase II or to use as an inhibitor an antisense molecule.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to manipulate the expression of a GCB by introducing an exogenous regulatory sequence.

Claims 127 and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aerts et al. in view of Smith et al. and further in view of Friedman et al.

The teachings of Aerts et al. and Smith et al. are outlined above.

Friedman et al. (US Patent 5,549,892, form PTO-1449 filed November 30, 2000, reference AD) teach remodeled recombinant human GCB produced in CHO cells. The sequence encoding human GCB comprises exogenous regulatory and coding sequences.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use recombinant GCB as a starting material for remodeling of carbohydrate chains in GCB. One skilled in the art would have been motivated to use recombinant and not naturally-occurring GCB in view of many advantages of the recombinant production of proteins over the traditional biochemical purification, such as much a large scale and standardized properties.

Claims 119, 121-126, 141, 142, 151, 152 and 158-162 are included in the 103(a) rejections because in view of their indefiniteness, *supra*, they are not limited by the exact numbers of percent, chains, mannose residues, etc. and the qualitative remodeling of GCB is obvious over the art.

Requirement for information

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application. The embodiment of "HT-1080 cells expressing Gene-Activated™ GCB" (page 51, line 16).

A complete reply to this Office action must include a complete reply to the requirement for information. The time period for reply to this requirement coincides with the time period for reply to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

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